IN THE TITLE

Please change the Title to read: --Methods Using Modified Vaccinia Virus--.

IN THE ABSTRACT

Please cancel the present Abstract and insert therefor:

--Disclosed is a method for producing a protein involving infecting a culture of eukaroyotic cells with a recombinant vaccinia virus.--

IN THE CLAIMS

Please amend the claims as follows:

Claim 25, line 2, please change "Kinase" to --kinase--.

Claim 28, line 1, please change "26" to --22--.

Claim 28, line 2, please change "glycoprotein" to --protein--.

Claims 30 to 32, line 1 of each, please change "28" to --29--.

REMARKS

Reconsideration and withdrawal of objections to and rejections of the above-captioned application are respectfully requested.

The title and abstract have been objected to (Office Action, at 2). Claims 22 and 24 to 32 were rejected under the judicially created doctrine of obviousness-double patenting as being unpatentable over claims 1 to 7 of U.S. Patent

No. 4,722,848 in view of Mackett el al. (AX) or Smith et al. (BT) (Office Action, at 2).

The specification was objected to under 35 U.S.C. §112, first paragraph and, claims 22 and 24 to 32 rejected thereunder because, in the Examiner's view the specification as originally filed fails to teach a method for the production of (i) any protein, (ii) any enzyme, (iii) thymidine kinase, (iv) any glycoprotein, (v) herpes simplex virus glycoprotein, (vi) influenza virus hemagglutinin, (vii) any antigen, (viii) any herpes simplex virus glycoprotein antigen, (ix) any influenza virus antigen, or (x) the hepatitis B virus surface antigen, which comprises infecting a culture of eukaroyotic cells with a recombinant vaccinia virus comprising DNA encoding the protein under suitable conditions to allow expression of the protein and, isolating the expressed protein from the cell culture (Office Action, at 3). The Examiner requested that the portions of the specification which support the claims be cited in response to this Office Action.

Claims 22, 29 and 32 were rejected under 35 U.S.C. §103 as being unpatentable over Smith et al. (BT) or Paoletti et al. (BJ) in view of Sofer et al. (Office Action, at 7-8). Claims 22, 24 and 25 were rejected under 35 U.S.C. §103 as being unpatentable over Mackett et al. (AX) in view of Sofer et al. and Bonnerjea et al. (Office Action, at 8). Claims 22, 26, 27 and 30 were rejected under 35 U.S.C. §103 as being unpatentable over

Paoletti et al. (BJ) in view of Bonnerjea et al. and Sofer et al. (Office Action, at 8-9). Claims 22, 26, 28 and 31 are rejected under 35 U.S.C. §103 as being unpatentable over Smith et al. (BS) in view of Sofer et al. and Bonnerjea et al. (Office Action, at 9-10).

A new title and abstract is supplied, without prejudice. The new title and abstract are based upon the former title and claim 22. No new matter is added. Reconsideration and withdrawal of the objections to the title and abstract are respectfully requested.

The references relied upon in the double patenting and obviousness rejections all have publication dates after December 24, 1981 and, should not be considered as prior art. Accordingly, the Section 112, first paragraph rejection shall be addressed with the art and double patenting rejections.

Indeed, it is noted that the present application is a division of application Serial No. 537,882, filed June 14, 1990, now U.S. Patent No. 5,110,587 ("the '587 patent"), which was a continuation of application Serial No. 090,209, filed August 27, 1987, which was a division of application Serial No. 622,135, filed June 19, 1984, now U.S. Patent No. 4,722,848 ("the '848 patent"), which was a continuation-in-part of application Serial No. 446,824, filed December 8, 1982, now U.S. Patent No. 4,603,112 ("the '112 patent"), which is a continuation-in-part of application Serial No. 334,456, filed December 24, 1981 now U.S.

Patent No. 4,769,330 ("the '330 patent"). The present application has the same specification as the '848 and '587 patents and, reference in the following discussion will be to text in the '848, '112 and '330 patents to show that the claimed invention is fully supported and entitled to a December 24, 1981 filing date.

Mackett (AX) was not available to the public until December 1982 such that it is not prior art as to the '330 patent and '112 patent specifications. Paoletti (BJ) bears a January 1984 date and is not prior art as to the '112 patent and '330 patent specifications. Likewise, Smith (BJ) was published in about April 1983 and is not prior art as to the '330 patent and '112 patent specification. Further, Sofer is dated in 1983 and cannot be prior art as to the '330 patent and '112 patent specifications. And, Bonnerjea is dated in 1986 and cannot be prior art to any of the present (or '848 patent), the '330 patent and the '112 patent specifications such that upon the showing below of support in the '848 and '112 patent specifications, the double patent and art rejections fail, as certainly as they do upon the showing below of support in the '330 patent specification. Thus, the Section 103 rejections are overcome by merely showing support in the '112 patent specification for the present invention (since primary and/or secondary references therefore fail to be prior art). However, support all the way back to the '330 patent specification is shown below.

Further, so that an appreciation may be had of the relationship among the present ('848 patent), '112 patent and '330 patent specifications, it is stated that it is believed that substantially nothing was deleted from the '330 patent specification in generating the '112 patent specification and, in generating the present application from the '112 patent specification, i.e., disclosure in each of the '330 patent and '112 patent specifications is in the present application.

The present claims are directed to a method for the production of a protein which comprises infecting a culture of eukaroyotic cells with a recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for the protein, under conditions suitable to allow expression of the protein, and isolating the express protein from the cell culture. Items (ii) to (x) of the Section 112, first paragraph rejection and objection are species within the generic concept of (i) protein.

Turning to the claims of the '112 patent, it is clear that the issue of a recombinant vaccinia virus comprising DNA encoding a protein was deemed to be disclosed and enabled in the initial ('330 patent) application. Claim 1 of the '112 patent calls for a recombinant vaccinia virus synthetically modified by the presence in a non-essential region of the vaccinia genome of DNA not naturally occurring in vaccinia virus. Claim 2 of the

'112 patent provides that the DNA is expressed in a host by the production of a protein. Claim 3 of the '112 patent provides that the protein is an antigen. Claim 4 of the '112 patent provides that the gene is from herpes simplex virus. Claim 6 of the '112 patent provides that the antigen of claim 3 is influenza virus hemagglutinin. Accordingly, the concept of present claim 22 and of the claims dependent thereon of a recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for a protein was already deemed to have been disclosed and sufficiently enabled in the '112 and '330 patents.

Further, it is additionally noted that the '848 patent (the present application) has also been deemed sufficient for the disclosure of a recombinant vaccinia virus synthetically modified by recombination to have within a non-essential region of the vaccinia genome a DNA sequence which encodes a protein. This is evident by claim 1 of each of the '848 and '587 patents. In this regard, it is further noted that claim 3 of the '848 patent illustrates that the application is enabled for a vaccinia virus synthetically modified by recombination to have, within a non-essential region of the vaccinia genome, DNA coding for an antigen. And, claims 4 to 6 of the '848 patent provide that the antigen (DNA coding) is for influenza virus hemagglutinin, hepatitis B surface antigen, and herpes simplex glycoprotein. Similarly, claims 2 to 4 of the '587 patent call for the protein

to be herpes simplex virus glycoprotein, hepatitis B surface antigen and influenza virus hemagglutinin.

Accordingly, it is clear that the present and predecessor applications provide support for the present claims which are patentable over the art of record with respect to a recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for a protein, as well as with respect to the recitations of the dependent claims. Thus, the steps of infecting a culture of eukaroyotic cells with such a recombinant vaccinia virus and, of isolating the expressed protein from the culture need only be shown in the present and predecessor applications.

Interestingly, starting from the end of the present specification (the '848 patent specification) and going to column 11, line 68 to column 12, line 21 of the '330 patent (with an intermediate stop at Examples of the '112 patent and, the disclosure therein prior to the Examples), it is clear that the present and earliest predecessor applications fully disclosed and enabled the method steps of infecting a culture of eukaroyotic cells with the inventive recombinant vaccinia virus and, isolating expressed protein from the cell culture. Before detailing this support, it is to be kept in mind that the ultimate purpose of the infecting and isolating steps, be it for harvesting the express protein or, for detection of expression by

the inventive vaccinia virus, is irrelevant. The method was fully disclosed and enabled in the present and earliest predecessor applications and, for either purpose, the method has utility.

Example XXXI of the '848 patent specification (i.e., the present specification (i.e., the present specification) is directed to expression of the HBsAg by vP59 in infected cells. The Example describes infecting monolayers of CV-1 cells with vP59. The nutrient medium was then collected, the cells were washed with saline solution, and the wash was combined with supernatant liquid. That paragraph at column 56, lines 49 to 56 of the '848 patent fully discloses and enables a method of infecting a culture of eukaroyotic cells with a recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for the protein, under condition suitable to allow expression of the protein, and isolating the express protein from the cell culture. The remaining portion of Example XXXI discloses how the collected fractions were assayed for HBsAg using an antibody-binding test.

Example XXXII of the '848 patent specification (the present specification) at column 57, lines 27 to 38 also discloses infecting CV-1 cells with vP11, harvesting the cells, freezing and thawing them to lyse them and, collecting and pelleting HBsAg from the supernatant liquid and, then assaying

using an antibody-binding test. In Examples XXXI and XXXII, the antibody-binding assay showed expression of the protein.

Continuing with earlier Examples in the '848 patent, Example XVII at column 44, line 43 to column 45, line 20 discloses the determination of expression of the HA gene by vP9 and vP10. Petri dishes containing eukaroyotic cells were infected with vP9 and vP10. The viruses were grown and, then contacted with H1 HA rabbit antiserum. The rabbit antiserum isolated the expressed protein from the infected culture of cells via binding. That isolated expressed protein was indeed isolated from the infected culture of cells is shown by the disclosed results of the radioautograph after contacting antibody-antigen complexes (formed from the isolation of the protein by the binding therewith of the antibody) with ^{125}I-labeled protein A.

Example XVII of the present (and '848 patent) application appears in the '112 patent at column 41, line 20 to 66. Moreover, Example XVII of the '848 patent and '112 patent specifications is based upon the general teachings which appear at each of: column 13, line 31 to column 14, line 33 of the '848 patent specification, column 20, lines 3 to 42 of the '112 patent specification and, column 11, line 68 to column 12, line 21 of the '330 patent specification. In each of the present and predecessor applications, there was full, enabling disclosure of creating plaques of recombinant viruses, i.e., infecting a culture of cells susceptible to vaccinia virus (eukaroyotic

cells), and isolating the expressed protein from that culture of cells by antibody-binding of the protein. Confirmation of the isolation of the protein, as well as of expression of the protein, is by autoradiography.

In this regard, with respect to the '848 patent, attention is also directed to the general discussion of Examples XXXI and XXXII at column 27, line 67 to column 20, line 3 and, the general disclosure of determining expression by vP9 and vP10 at column 20, line 19 to 63. That latter disclosure, i.e., a general description of the infection of eukaroyotic cells by vP9 and vP10 and the isolation from those cells of expressed protein also appears at column 20 lines 3 to 47 of the '112 patent.

Accordingly, a general description of the presently claimed method appeared in the disclosure of U.S. application Serial No. 334,456, filed December 24, 1981, as well as in application Serial No. 446,824 filed December 8, 1982. Further, the '112 patent specification (U.S. application Serial No. 446,824) as well as the present application contain not only that general disclosure of the method of the present invention; but also, specific Examples thereof (e.g., Example XVII in the '848 (present) and '112 patent specifications and Examples XXXI and XXXII in the present application).

Additionally, it is noted that the exogenous DNA in the inventive vaccinia virus is in a non-essential region of the vaccinia genome, i.e., it is in a portion of the genome which is

non-essential to the viability and stability of the virus. Thus, suitable conditions for the culturing of the eukaroyotic cells (conditions suitable to allow expression of the protein) are those which are suitable for culturing vaccinia virus (which were well known at the time of filing of the '330 patent specification because vaccinia virus had at that point been used for approximately 200 years in vaccines), as well as those conditions under which recombination takes place as disclosed at column 10, line 19 to column 11, line 2 of the '330 patent.

Likewise, the disclosure in the '330 patent with respect to growing vaccinia virus recombinants on selective media at column 12, line 22 *et seq.*, further shows that the earliest application as well as the present and intermediate ('848 patent and '112 patent) applications fully disclose conditions suitable to allow expression of the protein. Indeed, Examples XI and XII disclosed conditions suitable to allow expression of the coded protein from infecting a culture of eukaroyotic cells with a recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for the protein. Note again that the disclosure in the '330 patent appears in the present application.

Thus, the earliest ('330 patent), intermediate ('112 patent) and the present ('848 patent) application all fully support the presently claim invention. None of the references

applied in the provisional double patenting and art rejections are in any way prior art to the disclosures of the earliest ('330 patent), intermediate ('112 patent) and present ('848 patent) applications.

Accordingly, reconsideration and withdrawal of Section 112, first paragraph, double patenting and, Section 103 rejections are respectfully requested.

The specification was objected to under 35 U.S.C. §112, first paragraph and, claims 22 and 24 to 32 rejected thereunder because, while the Examiner recognized that a deposit under the Budapest Treaty was made, she asserted that it is not clear whether all restrictions imposed by the depositor on availability will be irrevocably removed upon the granting of a patent (Office Action, at 4-5).

The undersigned, an attorney who has signed papers and is therefore of record in the present application (See 37 C.F.R. §1.34; M.P.E.P. §402), hereby confirms that a deposit of the various constructs as set forth in the Preliminary Amendment was indeed made and, at the times of filing the parent applications (especially as shown by the text of those applications, namely the '330, '112, '848, and '587 patents). Access to the files of the predecessor applications by the Examiner for confirmation of deposit information during the prosecution of those applications is persumed. It is hereby confirmed that access to the deposits will be made available during pendency of the present application

to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C 122 and, that all restrictions imposed by the depositor on the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent from this application (including any Rule 62 continuation). The term of the deposit is at least 30 years from the date of deposit and at least five (5) years after the most recent request received by the depository for the furnishing of a sample of the deposit. In any case, the deposits are under agreements that would make them available beyond the enforceable life of the patent granted on this application (including any Rule 62 continuation). The deposits set forth in the application have been made under the Budapest Treaty.

OK

Accordingly, 37 C.F.R. 1.806 and, 1.808 are satisfied.

As to the Examiner's statement that "the deposit and declaration must have been filed at the time of filing the parent applications in order for the disclosure to be enabling for the constructs taught therein", it is respectfully stated that such is not correct. While the constructs were deposited under the Budapest Treaty at the time of the effective filing in the present and predecessor applications, MPEP §2406.01 and §2406.02 state that a deposit and, amending the specification to indicate the deposit, can be done after filing.

In view of the foregoing, reconsideration and withdrawal of the Section 112, first paragraph, rejection and objection are respectfully requested.

Claims 22 and 24 to 31 were rejected under 35 U.S.C. §112, second paragraph, because, in the Examiner's view, these claims are vague and indefinite in the recitation of a "protein", "enzyme", "glycoprotein", "herpes simplex glycoprotein", "influenza virus hemagglutinin", and, "antigen" because in each respective case the Examiner asserts that it is not clear which enzyme, glycoprotein, herpes simplex glycoprotein, influenza virus hemagglutinin or antigen is intended (Office Action, at 5-7). Additionally, as to claim 22 the Examiner asserts that the claim is vague and indefinite in the recitation of "under suitable conditions to allow expression of the protein" because in the Examiner's view it is not clear what culture conditions are intended. Additionally, the Examiner asserts that claim 22 is vague and indefinite in the recitation of "isolating the expressed protein from the cell culture" because it is not clear what procedures are intended. As to claim 25, the Examiner is unclear as to why "Kinase" has been capitalized and, as to claims 27 and 30 and, 28 and 31, the Examiner has inquired whether these claims are not duplicates.

With the respect to claim 25, "Kinase" has been amended to read --kinase--. Additionally, as to the apparent confusion between claims 27 and 30 and between 28 and 31, claims 30 to 32

have been amended to depend upon claim 29 and, claim 28 has been amended to depend upon claim 22. The protein of claim 22 can be an enzyme such as thymidine kinase as well as a glycoprotein or an antigen. The protein of claims 30 to 32 are antigens by virtue of dependency upon claim 29. Thus, the distinction between claim 27 and claim 30, as well as between claim 31 and claim 28 is that the proteins of claims 30 and 31 are antigenic whereas those of claims 27 and 28 need not be.

With respect to the remainder of the Section 112, second paragraph, rejection, it is respectfully submitted that this rejection is in essence merely a back door attempt to unduly limit the claims to only disclosed embodiments, i.e., an improper Section 112, first paragraph, rejection which has also been improperly stylized as a Section 112, second paragraph, rejection. Nonetheless, as discussed above with respect to the Section 112, first paragraph objection and rejection, the double patenting rejection, and the art rejections, it has already been determined that the disclosure of the present and predecessor applications is sufficiently clear and definite in regard to the recitation of "protein", "enzyme", "glycoprotein", "antigen", "herpes simplex glycoprotein" and "influenza virus hemagglutinin".

In particular, as discussed above, claims of the '330, '112, '848 and '587 patents employ the terms "protein", "antigen", "herpes simplex glycoprotein" and "influenza virus

hemagglutinin" and, the term "protein" is a genus which includes: "enzyme", "glycoprotein", "herpes simplex glycoprotein" and "influenza virus hemagglutinin". Accordingly, the claim terms are clear and definite.

Additionally, as to the recitation of "isolating the expressed protein from the cell culture", as discussed above, methods for performing the "isolating" step are fully disclosed in the present application and, are also fully disclosed in the predecessor applications, such that the claim term is quite clear and definite. The skilled artisan at the time of the filing of the earliest application understood what is meant by "protein", "suitable conditions to allow expression of the protein", "isolating the expressed protein", "enzyme", "glycoprotein", "herpes simplex glycoprotein" and "influenza virus hemagglutinin". No further or more specific recitation of particular "proteins", "enzymes", "glycoproteins" or "conditions" for "expression" or "isolation" need be detailed. The present invention is a pioneer invention and Applicants may so claim it broadly. Indeed, that Applicants may claim the present invention broadly has been already determined in Applicants' favor virtue of the language of the claims of the issued patents in the lineage of the present application.

While the term "pioneer" usually arises in connection with whether infringement will be found under the doctrine of equivalents, in the patent prosecution context the Court of

Customs and Patent Appeals has stated that the pioneer status of an invention allows for broad claims to the broad concept of the invention. In re Hogan, 194 U.S.P.Q. 527, 537 (C.C.P.A. 1977).

In Hogan, Hogan et al. had filed a 1953 application disclosing a solid polymer produced from 4-methyl-1-pentene. The only method disclosed entailed the production of a crystalline polymer. During 1962 another applicant disclosed that an amorphous form of the polymer could be produced. The PTO asserted that the Hogan et al. application only enabled claims to crystalline polymers, not claims which dominated a solid amorphous polymer. Claim 13 of Hogan et al. read simply: "A normally solid homopolymer of 4-methyl-1-pentene."

On the issue the Court stated:

> Rejections under §112, first paragraph, on the ground that the scope of enablement is not commensurate with the scope of the claims, orbit about the more fundamental question: To what scope of protection is this applicant's particular contribution to the art entitled.
>
> Though we do not reach the point on this appeal, we note appellants' argument that their invention is of "pioneer" status. The record reflects no citation of prior art disclosing a solid polymer of 4-methyl-1-pentene, which may suggest that appellants at least broke new ground in a broad sense. On remand, appellants may be found to have been in fact the first to conceive and reduce to practice "a solid polymer" as set forth in claim 13. **As pioneers**, if such they be, **they would deserve broad claims to the broad concept**. What were once referred to as "basic inventions" have led to "basic patents," which amounted to real incentives, not only to invention and its disclosure, but

> to its prompt, early disclosure. If later states of the art could be employed as a basis for rejection under 35 U.S.C. 112, the opportunity for obtaining a basic patent upon early disclosure of pioneer inventions would be abolished.
>
> The PTO has not challenged appellants' assertion that their 1953 application enabled those skilled in the art in 1953 to make and use "a solid polymer" as described in claim 13. Appellants disclosed, as the only then existing way to make such a polymer, a method of making the crystalline form. To now say that appellants should have disclosed in 1953 the amorphous form which on this record did not exist until 1962, would be to impose an impossible burden on inventors and thus on the patent system. There cannot, in an effective patent, be such a burden placed on the right to broad claims. **To restrict appellants to the** crystalline **form disclosed,** under such circumstances, **would be a poor way to stimulate invention, and particularly to encourage its early disclosure. To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws.** See In re Goffe, 542 F.2d 564, 191 USPQ 429 (CCPA 1976).

194 U.S.P.Q. at 537 (emphasis added).

Applicants, pioneers, broke new ground in a broad sense because it is Applicants who first taught a recombinant vaccinia virus, infecting with such a virus and isolating the protein expressed therefrom. As pioneers, Applicants deserve broad claims to the broad concept, without unnecessary limitations for terms which are well understood in the art and have been

permitted in the claims of the applications which issued in the lineage of the present application.

As to the scope of the claims, they are allowable. Applicants have discovered a pioneer invention and are entitled to claims as broad as the art permits. Indeed, to limit Applicants to their disclosed embodiments is improper, as per In re Goffe, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976) wherein, in reversing such a rejection as erroneous, the Court stated:

> For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials . . . would not serve the constitutional purpose of promoting progress in the useful arts.

Further, as discussed above, the claims are commensurate in scope with the disclosure.

Reconsideration and withdrawal of the Section 112, second paragraph, rejection are respectfully requested.

Return of the PTO-1449 is acknowledged and, Applicants will provide with a separate paper a copy of the documents which were of record in the predecessor applications but, which the Examiner apparently cannot the locate from those files, as well as any additional documents which may be of interest.

Moreover, in view of the amendments and remarks herewith and the disclosures of the parent and predecessor applications, the present application is in condition for allowance. Favorable reconsideration of the application, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

CURTIS, MORRIS & SAFFORD
Attorneys for Applicants

Thomas J. Kowalski
Reg. No. 32,147
(212) 840-3333